

HEREDITARY MULTIPLE TELANGIECTASIS.

by

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CONGENITAL AND FAMILIAL TELANGIECTASIS.

Congenital and Familial telangiectasis is a disease of the circulatory system, affecting the capillaries and venules.

* This disease is considered to be a very rare one inasmuch as it is mentioned in very few, if any, of the standard textbooks on Dermatology or Medicine. This may be due to the fact that it rarely causes symptoms except when the nasal and buccal mucous membranes are affected and haemorrhage takes place. The disease may be confined to the skin alone, but it may be localized to a definite part of the body, such as the chest, arms, legs, or back. In such cases haemorrhage may never take place, and the only manifestation of the disease is the small cherry red spots of varying sizes up to about two or three millimetres in diameter, or the presence of spider naevi as in a case described by Williams¹:-

A boy of $10\frac{1}{2}$ years came into the office, by accident, with a typical spider naevus a little beyond the outer canthus of the right eye. It had been present three or four years and was gradually increasing. He also had a rather pale, flat naevus on the left upper eyelid. This had not been noticed by the mother and its duration was uncertain. This child/

child had had no nosebleed. Two brothers had had nosebleed, but no telangiectasia, while the fourth child, a girl, was exempt. The mother of these children had suffered frequently from nosebleed, and had severe spider naevi on the face, which had been removed several years before the visit; while her mother suffered frequently from nosebleed and had many small dilated veins on the face in adult life.

Williams¹ gives the essentials of the disease as follows:

- (1) The occurrence of nosebleed in childhood, often recurring throughout the life of the patient, and sometimes associated with bleeding from other mucous membranes, or even, after traumatism, from the skin. The bleeding may decrease as the patient grows older, or may become more and more serious and finally prove fatal.
- (2) The development of telangiectases, sometimes as dilated capillaries, sometimes as a network of dilated venules, more characteristically as spider naevi; occurring sometimes in youth, more often in adolescence or adult life, and usually increasing with the passing of years.
- (3) The occurrence of these symptoms in several members of the family. Usually the same individual presents both groups of symptoms, but sometimes one group or the other may be missing in an individual case.

His case already quoted shows this characteristic, as one boy had spider naevi but no history of nose-bleed, while the other two brothers had had nosebleed but no telangiectases. It will be interesting to watch these children to see whether they develop more lesions in adult life. The following he gives as a classic case of hereditary telangiectasia.

On January 11th 1926, there came to my office a woman, aged 56 years, whose face was literally studded with telangiectasia, the lesions varying from dots hardly more than one millimetre in diameter to dusky red patches four to five millimetres in diameter, at the borders of some of which were radiating venules. Some of the lesions presented a fairly uniform colour; others consisted of a network of dilated venules; still others were typical spider naevi. Most of the spots were smooth and level with the skin, while others were slightly elevated. Besides the face, the ears, and the sides of the neck were affected. There were red spots also on the mucous membranes of the cheeks, gums, and hard and soft palate, and a very few on the forearms. The rest of the body was free. The nasal mucous membrane was not examined. Questioning elicited a history of nosebleed from childhood. The telangiectasiae were first noticed when patient was 21 years old, and were then very small. They increased gradually, more rapidly after the/

the birth of her two children, who are now 27 and 28 years old, and still more rapidly during the past four or five years. In answer to direct questions, the patient stated that a cut would always bleed freely, but heal promptly. However, as there seems to have been no excessive bleeding at parturition, it is doubtful whether there is any real haemophilia. There was no history of blood in the stools or in the urine. The patient was in good health and came only for a diagnosis. She declined any operative treatment for the telangiectasia. Her father and her oldest brother had a similar condition, while her mother, her twelve brothers and sisters and her two children were exempt as far as she knew. The affected brother has no children and she herself has no grandchildren.

This third case by the same author shows that the disease may subside as the patient gets older, with disappearance of the epistaxis.

A man, aged 50 years, came to the dispensary for an eruption of the hands, which proved to be dermatophytosis. On the right cheek, below and behind the outer canthus, was a typical spider naevus, and on questioning a history was obtained of profuse and frequent nosebleed, up to the age of 17 years. No history could be obtained of the occurrence of the disease in any other member of the family, but the man/

man was an Italian, who spoke very little English, and the disease might well have been present in his family without his knowledge.

Williams¹ collected four cases complete in every respect, and a fifth in which only the family history was lacking, all observed within four weeks.

Goldstein² says that strictly speaking telangiectasis is a dilatation of the terminal vessels, - i.e. capillaries - but that it is a term used also to describe dilated venules. It involves the skin and mucous membranes of the nose and mouth, but may affect also the cheeks, ears, tongue, lips, fingers, and other parts of the body. He states that this rare affection is associated with recurring epistaxis of the familial type.

Hanes³ defines the condition as a hereditary affection, manifesting itself in localized dilatations of capillaries or venules, forming distinct groups or telangiectases, which occur especially on the skin of the face, and the nasal and buccal mucous membranes, and give rise to profuse haemorrhage, either spontaneously or as the result of trauma.

CLASSIFICATION.

The disease has been divided into two types:-

- (1) Inherited.
- (2) Acquired.

Goldstein/

Goldstein² further divides the telangiectases with epistaxis principally into three forms:-

- (1) Pin-point.
- (2) Spider - the most common.
- (3) Nodular.

He finds spider naevus is often associated with cirrhosis of the liver. The spots are from two to three centimetres in diameter, and consist of a central dot towards which some vessels converge.

Nodular forms are supposed to occur sometimes with cancer of the abdominal organs, especially of the stomach.

Steiner⁴ classifies the types of this disease similarly and says that the telangiectases seen are of three types: the pinpoint, which is apt to be seen on the skin of the hands and face, and which may be readily overlooked; the spider form; and the nodular type, which may originate in the centre of a spider and form a solid vascular tumour about the size of a split pea.

AETIOLOGY.

The aetiology of the disease is obscure. The following are the principal aetiological factors which are associated with the disease.

HEREDITY. /

HEREDITY.

The one outstanding factor, on which all writers are agreed, is its hereditary nature.

Hanes³ believes that the three factors of aetiological import are:

- (1) Heredity.
- (2) Repeated traumatisms.
- (3) The abuse of alcohol.

The hereditary tendency to the disease being by far the most striking and constant feature. He says that both as to formation of telangiectases and epistaxis, this is the only factor constantly present.

Goldstein² published an extensive biography of this disease. He collected from literature the reports of thirty families affected by this condition and added another family to the group. He finds that the tendency to recurring nasal haemorrhages (familial in type) is a prominent feature, and there is a hereditary history of recurring haemorrhages and telangiectases in the family.

The case already described by Williams¹ would never have been diagnosed had the family history not been gone into. He believes that the disease is exceedingly common, and that its frequency will be established if every physician who sees a spider naevus will ask about the occurrence of nosebleed in/
in/

in the patient and in others of the family. The condition is supposedly so rare that only about thirty-three families are reported in medical literature. As Williams says it is altogether probable that many cases are overlooked for lack of proper questioning.

Steiner⁴ opines from a consideration of the histories of the families affected with haemorrhagic telangiectasis which he has investigated, and from those previously recorded, that we may conclude that heredity is the only important aetiologic factor as yet discovered. He adds that in its causation, the hereditary tendency is the only factor which is constantly present, although others, such as syphilis, alcohol and traumatism have been irregularly reported.

MacCullum⁵ states that many of the spots are found in the neighbourhood of angles or fissures about the face and neck so that they have been thought to be congenital displacements.

Legg⁶ thought the condition was due to congenital weakness of the vessels, which remained permanently in a stage of early formation.

Weber⁷ concludes that the morbid syndrome is not connected with any haemophilic tendency or any diminution of blood coagulability.

It is possible that the reason why many cases may be missed or never diagnosed is that the epistaxis may be so mild that the patient takes no notice of it and/

and not considering it a manifestation of disease never consults his or her doctor about it.

INFLUENCE OF SEX.

The cases of this disease which have been reported tend to show that neither sex is more liable to the disease, and that both are equally capable of handing it on.

Weber⁷ concludes that the disease affects and is transmitted by both sexes.

Steiner⁴ remarks that its incidence among the sexes is probably about equal, and that both sexes are able to transmit it.

East⁸ says that in the reported cases, 104 are males and 108 are females. The disease seems to be transmitted rather more often by females than males.

Goldstein² is of the opinion that males and females are affected alike and are equally capable of transmitting the disease to their offspring. He adds that there is probably a preponderance of females over males in connection with the development of generalized and localized telangiectasia.

RACIAL.

East⁸ remarks that the majority of the families belong to the Anglo-Saxon race.

ACQUIRED. /

ACQUIRED.

Several cases are on record which are not altogether typical of the hereditary type. These may be of the acquired variety, but histories are often so difficult to obtain that a hereditary factor may be present and the following factors are only aggravating or incidental.

Stokes⁹ has written an interesting article showing that syphilis, chronic plumbism, hyperthyroidism, and nephritis may cause cardio-vascular degenerative conditions which result in the formation of generalized telangiectasia. Out of thirty-three cases which he found in his search he noted that syphilis, plumbism, hyperthyroidism, or nephritis was present in twenty-two and possibly in twenty-three of them.

Hanes³ has shown, that the telangiectases are generally localized at parts most subject to frequent traumatism. The bleeding in these cases is often so severe that a condition of marked anaemia is induced, which may be an important factor in the development of the telangiectases.

Goldstein² holds that syphilis, alcohol, and other infections or intoxications do not appear to have any definite relation to this condition, but that telangiectases, symptomatic of disturbance of the general circulation are not infrequent. Either when/

when the heart itself is at fault, or when some distal portion is involved, sometimes by disease of the lungs, spleen, liver, or thyroid. In exophthalmic goitre the circulation may be disturbed considerably and telangiectases may form. He further states that telangiectases of the skin are frequently found in apparently normal persons and have no pathological significance. However, they may develop in large numbers of varying sizes on the skin of persons with diseases of the pancreas and liver, - cancer, chronic jaundice from gall-stones, or simple catarrhal jaundice, also in tertiary syphilis, and as a result of exposure of the skin to the röntgen ray. He admits, however, that cardio-vascular degenerative conditions (syphilis being the most important) appear to have some aetiologic relationship in a few of the reported cases of telangiectasia. In some cases lead, alcohol, hyperthyroidism, dyspituitarism, many of the infectious diseases, particularly syphilis, may have an aetiological relationship.

Majocchi¹⁰ believes that there is some direct action of some toxin on the vessels which excites endothelial reaction and proliferation and brings about this condition.

Head¹¹ reported two cases of multiple haemangiomas of the skin associated with dyspituitarism.

Case I./

Case I.

A Swedish farmer, ^{*}single, aged 28 years, gave no history of venereal disease. He had been sick since 8 years of age. The telangiectases appeared when he was 14 years old, on the penis and scrotum, later, on the thighs, arms, back and abdomen. No lesions were seen on the mucous membrane of the lips, mouth or nose. There were some telangiectases on the face and neck varying in size from pinpoint to two millimetres in diameter. The Wassermann test was negative; no glycosuria; no epistaxis; pains in the toes and fingers and dull aches in the knees. Four brothers and three sisters are well. Mother died of apoplexy.

Case II.

A man, aged 60 years, labourer, with no history of venereal disease or nosebleed, had haemangiomas of the skin of the scrotum and mucous membrane of the cheeks and lips. He suffered from acromegaly and had mitral endocarditis. Family history was negative. Father and brother died of tuberculosis. The Wassermann test was negative.

* In this case Head¹¹ omitted the type of dyspituitarism in the patient.

PATHOLOGY.

Site. The commonest sites in which the telangiectases are found, are in the skin and the mucous membrane of the septum of the nose, although they may appear on any part of the body.

The nose need not necessarily be affected as will be seen in the discussion on symptoms. As epistaxis is the important factor which brings the case under observation as a rule, this site may have received undue prominence. Lesions in other parts causing no symptoms are very liable to pass unheeded.

MacCullum⁵ writes that these tumours occur most commonly in the skin, especially on the face and scalp, but also in all other parts of the body. Other examples of simple angiomas are found in the muscles, where they reach a considerable size. In the tongue, nose, and lips they are also found, but in all these latter situations the tumour is likely to have more of the cavernous character.

East⁸ states that the spots are distributed chiefly on the face, especially on the cheeks and nose. They occur very constantly on the septum of the nose low down in front. The commonest site on the body is on the hands and under the nails.

According to Goldstein² the multiple telangiectases most commonly occur on the buccal and nasal mucous /

mucous membranes and lips and face. They have been noted on the feet, hands, ears, scalp, neck, forearms and chest. He concludes that the lesions of dilated capillaries are confined largely to the skin of the face and the mucous membranes of the mouth and nose.

GENERAL PATHOLOGY.

According to MacCullum⁵ a haemangioma is a tumour composed, essentially of blood channels. A true haemangioma is distinguished from a mere dilatation of capillaries or venules belonging to the general circulation by the fact that its blood channels grow independently, without regard to the laws which govern the distribution of such vessels. It thereby forms a mass which is somewhat withdrawn from the general circulation and although supplied with artery and vein, does not stand in any intimate anastomotic relations with the adjacent circulation. Ribbert³⁰ lays great stress upon this lack of communication between the capillaries of an angioma and those of the contiguous tissue, and has proved his point by injections. Further, he insists that such tumours grow from their own vascular substance, and not through the widening and assimilation of adjacent vessels. There are some border-line forms in which it is difficult to say whether one is dealing with a tumour or not, such as the plexiform or cirroid angiomata/

angiomata of the scalp, which is made up of tangled masses of pulsating arteries, and others of even less tumour-like nature, such as the bluish vascular flecks seen in the skin of old people.

True haemangiomata are most commonly divided into a simple or telangiectatic form, in which the abundant capillaries, though widened, maintain fairly well their form as tubes with parallel walls, and the cavernous form, in which the character of erectile tissue is approached, with large, irregular blood-spaces opening abundantly into one another. It is not very apparent, however, where the line of division can be sharply drawn between these groups. Certainly it is difficult to determine from sections in some cases whether one should regard the tumour as verging on the cavernous or not.

The more definitely simple forms through which blood runs fairly rapidly present themselves as flat or slightly elevated, bright-red patches from which the blood may be squeezed out.

MICROSCOPIC PATHOLOGY.

Hanes³ removed tissue from a telangiectatic spot. This showed obliteration of the papillae of the corium, together with the absence of the usual undulations of the stratum germinativum. This was doubtless due to the relatively enormous dilatation/

dilatation of the blood vessels of the corium, which are seen as wide spaces, lined by a single layer of endothelium lying immediately subjacent to the greatly attenuated epidermis. These dilated vessels can be traced well down into the subcutaneous fatty tissue.

A study of suitably stained sections failed to reveal any muscular or elastic tissue in the walls of the dilated superficial vessels, although the less dilated vessels in the subcutaneous fatty tissue showed the normal arrangement of the tunicae.

Hanes³ refers to the insufficient protection of the dilated vessels and states that it is not surprising that trivial traumatisms produce marked haemorrhage.

Steiner⁴ says that microscopically a developmental defect has been found in the dilated capillaries, as the elastic and muscle fibres appear to be wanting. The capillaries, consequently, are very liable to produce haemorrhage by their rupture, which is induced either spontaneously or by traumatism.

East⁸ writes that the disease is due to a familial tendency for defects to appear in the small bloodvessels.

The changes then consist in a dilatation of the capillaries and the small veins, with the formation of telangiectases. These dilated vessels being only lined by endothelium without the additional presence of elastic or muscle fibres, become consequently very/

very liable to rupture, induced either spontaneously or by trauma.

SYMPTOMS.

Multiple telangiectases constitute the sole characteristic of this disease. This is the primary lesion while all other symptoms and signs are secondary manifestations.

Goldstein² says that haemorrhage is the one constant symptom of the disease and the source of all the other symptoms. Secondary anaemia may become quite serious. Among the most striking characteristics of the disease is the tendency to affect more than one member of a family, and the marked tendency of a large number of the patient's relatives to have suffered from epistaxis for many years.

In 1865 Babbington¹² reported an interesting family in which recurring epistaxis had been observed for four generations. The transmission was through both male and female, but no mention was made of telangiectases in any of them.

He also reported a case of hereditary epistaxis in a native of Lincolnshire. The patient had been subject to frequent and violent attacks of epistaxis during all her life. She had four children, two of whom (man and woman) likewise had habitual and severe attacks of epistaxis.

Rendu¹³, however, was the first to associate the presence of epistaxis with multiple telangiectases as clinical manifestations of a distinct morbid entity.

Because of the frequency with which the mucous membrane of the septum of the nose is affected epistaxis becomes a pronounced symptom of this disease.

East⁸ tells us that the marked symptom of the condition is epistaxis, coming from the lesions in the nose or bleeding from similar lesions elsewhere.

The nasal mucous membrane is not necessarily always affected, as was shown in that case of Williams¹ where the boy had spider naevi on his face but no epistaxis. Then again it apparently may be the only part affected as in the case of the two boys, quoted by the same author, who had epistaxis and no sign of any telangiectases. Spots in these cases may of course appear later on.

Ballantyne¹⁴ also reports a case of a boy who had no spots but bled from the nose.

East⁸ says that occasionally spots are present but no epistaxis occurs, as is shown in his case of a girl, the daughter of a woman with the disease, who has several spider naevi scattered over the body; she has never had epistaxis and she says the spots come and go quite quickly. There are none on her face. A sister of the same woman has a few telangiectatic spots on the bridge of her nose; she has never had/

had nosebleeding. Two of her children, both under 14 years of age, have naevi on the nose and face but neither has had nosebleeding.

Kennan¹⁵ reports 6 cases in which no bleeding occurred from anywhere except the nose. There was no history of the occurrence of telangiectases in any of them.

Hanes³ also reported a case of two brothers who both had nosebleed but neither had telangiectases in other sites.

In the family reported by Babbington¹² there was no mention of any telangiectases although there was recurring epistaxis.

Weber⁷ concludes that the haemorrhage in most cases is only from the nasal mucous membrane; but in some cases takes place also from the lesions on the tongue, fingers, and cheeks.

Goldstein² informs us that in the great majority of cases haemorrhage occurs in the form of epistaxis. Haemorrhages may occur from the telangiectases on the tongue, lips, fingers or buccal mucous membrane and even rectal bleeding may occur. In one of his cases haemorrhage occurred in the brain, causing temporary hemiplegia and other symptoms of apoplexy.

According to East⁸, bleeding chiefly occurs from the spots in the nose, but it not infrequently starts from the mouth during eating and sometimes from the face/

face or elsewhere if a spot is damaged.

Haemorrhages may, of course, occur from any part of the body in which the angiomas are present and is usually due to trauma. In one of Hanes'³ cases, that of a man, 33 years old, not subject to recurring epistaxis, but who had severe haemorrhages from telangiectases on the lips, and tongue, and from under the nail on the left middle finger. He however occasionally bled from the nose.

Fox¹⁶ reports the case of a woman who had epistaxis for 10 years, who recently began to have bleeding from the rectum. Sigmoidoscopy showed that the lower bowel was normal.

Josserand¹⁷ describes a woman, aged 56 years, who had suffered from epistaxis since childhood. Lately she also bled from the lips, gums, and tongue. She exhibited telangiectases on her neck, chest, back and arms, but in greater numbers on the face, lips, tongue and palate.

Gjessing's¹⁸ case, a man of 51 years, bled from the nose and the spots on the cheeks, eyelid, and tongue.

Sequiera¹⁹ reports a case where spots on the left index finger bled spontaneously several times in the course of three or four years. She had had attacks of epistaxis for several years before.

Anderson's²⁰ /

Anderson's²⁰ case was a boy on whom angiomas first appeared at the age of 11 years. He had rectal bleeding.

The case given by Ullmann²¹ is an excellent example to show that there is probably no part of the body which may not be affected with telangiectases.

A woman, aged 40 years, had roundish purplish angiomas on the face varying in size from a hempseed to a small pea. Haemoptysis occurred. The patient died of pneumonia. At the necropsy angiomas were found in the skin, respiratory mucous membrane, rectum, urethra, and liver. No mention was made of any of her relatives being similarly affected or as suffering from epistaxis.

One of Dr Osler's²² patients at the necropsy revealed a dozen round foci, each from three to four millimetres in size, which at first looked like ecchymoses, but were dilated capillaries and venules, in the stomach. The sections of the septum of the nose showed large dilated veins just beneath the epithelium.

Steiner⁴ sums up by saying that the chief symptom is haemorrhage, which may come from the telangiectases in the nose as an epistaxis or from those situated elsewhere. These locations are the conjunctivae of the upper and lower lids, the ears, cheeks, nose, lips, /

lips, mucous membranes of the mouth in the region of the hard and soft palate, the uvula, buccal mucous membranes or gums, tongue, neck, trunk, back, arms, finger tips, under the nails or on the feet.

NATURE OF HAEMORRHAGE.

Bleeding varies greatly in frequency.

It may occur three or four times daily, once or twice a week, or there may be even greater intervals of freedom.

Haemorrhage varies in severity, may be very slight or so severe as to cause death from syncope. Some cases of death from this cause have been reported.

Less severe bleeding has produced, by the resulting anaemia, vertigo, headaches, weakness, dyspnoea on exertion, palpitation and swelling of the ankles, oedema and heart failure.

ONSET OF SYMPTOMS.

One of the peculiarities of this disease is that the onset of the nosebleeding is usually in early childhood and that the telangiectases appear on the skin at a much later date, the interval being very variable, up to a number of years. In the majority of cases also the severity of the bleeding and the number of the angiomas tend to increase with the passing of years up to about forty, when it is generally at its worst and treatment is sought on account/

account of the epistaxis or the symptoms due to it.

Telangiectases may nevertheless be seen in early life.

East⁸ writes that in the majority of cases there is a history of bleeding from the nose, starting in childhood. Often in childhood the spots are not at all conspicuous and they become more prominent as the patient grows older. Epistaxis is then the only symptom. When the lesion appears later in life the epistaxis starts with the appearance of the spots. He is of the opinion that if the individuals pass the age at which the lesions usually come without them appearing they seem to escape altogether. He considers the usual age to be about twenty-three years.

Hanes³ has seen them in a boy of eight years.

Crocker²³ reported a case in a girl, seven years of age, with an enormous number of dilated vessels first observed at five years of age and occurring on the face, back of forearm and hand.

In Anderson's²⁰ case, angiomas appeared at eleven years.

Weber⁷ says that in most cases a tendency to nose bleeding has been present from early life, or, at all events, many years before cutaneous angiomas were observed. He further states that with advancing years attacks of haemorrhage and the anaemia become more severe.

Goldstein/

Goldstein² has found that the lesions in the hereditary group of cases are more apt to become prominent and increase in numbers between the ages of thirty-five and fifty years. Most of these patients suffer from symptoms of profound secondary anaemia.

Laffont's²⁴ patient was a woman, aged forty-eight years, who noticed at the age of thirty-nine to forty years that telangiectases were appearing on the scalp, face, ear, breast and back. Some had disappeared spontaneously. Since puberty she had repeated attacks of nosebleeding.

Gjessing's¹⁸ case, already referred to, of a man of fifty-one years, had severe epistaxis since childhood, and it was not till about twenty-five or thirty years of age that he noticed telangiectases appearing on his face and mucous membrane of his mouth. Next they appeared on the ears, under the chin, on the neck, nose, tongue, hard palate, and the right lower eyelid, a few spots developing on several fingers, and the left arm.

In Williams'¹ classical case the spots first appeared at twenty-one, although the patient had nosebleed all her life.

Weber⁷ in his conclusion says that the cutaneous angiomas usually first attract attention towards middle life.

Steiner's/

Steiner's⁴ cases, given below, go to show that the haemorrhages from the nose are generally seen early in life, while the telangiectases are a later development.

The epistaxis, starting in early childhood usually becomes more severe and prolonged as the patient advances in years, the period between thirty-five and thirty-eight years of age being the time when the increase is specially noted. The following cases by Steiner⁴ illustrate this:

Case I.

Patient was fourteen years of age when frequent epistaxis started. Recurred weekly, or at more frequent intervals. When sixteen years old slight haemorrhage from a small red spot on his face occurred. There was never any additional haemorrhage noted from his mouth or rectum, and the urine never contained blood.

Case II.

A woman had epistaxis ever since she could remember, which begins and stops spontaneously. Intervals between the bleedings have varied from three to four weeks up to two or three months. Married for ten years, and has had three children, no excessive bleeding at parturition. Subsequently the bleeding increased in severity so that the patient has occasionally/

occasionally been much prostrated by the secondary anaemia induced.

Case III.

Began to bleed from her nose at sixteen years of age. Has had five haemorrhages from the tongue. Later on the bleeding especially from the nose increased in severity.

Case IV.

At the age of twenty-five years the patient began to have attacks of epistaxis the day preceding the onset of each menstrual flow. Fifteen years later she began to have spots on her cheeks. Two years later she noticed them on her hands and wrists. for the past week she has had one to three attacks of severe epistaxis daily.

Hanes³ has written that "Certain it is that the bleeding generally precedes the formation of the localized dilatations of the capillaries and venules, and may do so with many years intervening between them. In some cases, also, a respite from the bleeding appears to be coincident with the disappearance of the telangiectases."

This reference to the bleeding preceding the dilatations of the vessels must, of course, relate to the vessels of the skin, - the epistaxis coming from telangiectases in the mucous membrane of the septum of the nose. These must have been present initially.

DIAGNOSIS.

The diagnosing of a case of hereditary telangiectases should present no difficulties.

Williams¹ believes that the hereditary character is necessary for diagnosis, and it is precisely this feature which is sometimes difficult to establish.

DIFFERENTIAL DIAGNOSIS.

The diseases which may be confounded with this one are:

Haemophilia; Purpura; Scurvy; Pernicious Anaemia; or the "Phthisical state with haemorrhages". High Blood Pressure.

HAEMOPHILIA.

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Before Rendu's time the disease was generally considered haemophilia.

The clotting time of the patient's blood in hereditary telangiectasis has always been found to be normal, and there has been no history of haemophilia in the families. This proves telangiectasis to be a distinct disease from haemophilia.

In telangiectasis males and females are equally affected, whereas the males are usually entirely affected in haemophilia.

The latter disease is also only transmitted through the female branches, while telangiectasis can be derived from either parent.

PURPURA.

In this disease haemorrhage occurs under the skin and produces blotches of a more or less purple colour. This never occurs in telangiectasis.

Purpura usually arises as a direct result of poisoning from without, e.g. overdosing with Potassium iodide, phosphorus, and from the commercial use, (handling and inhalation), of benzol or its chief constituent benzene.

There is no history of heredity, and the spots do not disappear on pressure.

Rheumatism being the most frequent cause of purpura there is usually a history of this disease.

Purpura haemorrhagica usually affects delicate children and is more common in girls.

SCURVY.

In this disease there is a history of some deficiency in the food eaten by the patient for some time before the symptoms appear. The gums are markedly affected and the bleeding takes place from them and not from the nose. There may also be haemorrhages under the skin and under the periosteum of the long bones, especially in the limbs.

PERNICIOUS ANAEMIA.

In this disease epistaxis is not at all a pronounced symptom. In telangiectasis the blood picture/

picture is that of a simple secondary anaemia, with a low colour index. In pernicious anaemia the blood picture is distinctive, showing abnormal cells, such as normoblasts, megaloblasts, megalocytes, etc. The colour index is also always above one.

PHTHISICAL STATE WITH HAEMORRHAGES.

The finding of evidences of phthisis in the lungs immediately gives a clue to the trouble. The two diseases may however be co-existent in the same individual. A good example of this was given by Mekie²⁵ who reported a case of a man aged 38 years suffering from advanced tuberculosis of the lung. He exhibited numerous telangiectases over his face and body. The history of epistaxis since he was 15 years old, and the hereditary nature as shown by the family history, leaves no doubt in the diagnosis of hereditary telangiectasis.

HIGH BLOOD PRESSURE.

Epistaxis sometimes occurs in this condition. The blood pressure is always found to be above the average for the age of the patient and other signs and symptoms of high blood pressure are present. In telangiectasis the blood pressure is about 130. In none of the cases reported was it above 145.

PROGNOSIS. /

PROGNOSIS.

The tendency of the disease to become worse with age makes it one of comparative seriousness, and Steiner⁴ considers that the outlook is not good as haemorrhages are apt to increase in severity as middle life is reached. In one case, however, there was a cessation of the bleeding as this period was approached.

The haemorrhages may be the cause of death, or result in much invalidism, while some cases are not much incapacitated by them.

TREATMENT.

This is purely symptomatic.

Thermocautery is probably the best treatment. Hanes³ used a bead of chromic acid, fused on a probe, with excellent results. Repeated cauterizations may be necessary within the nose.

Bruck²⁶ has used the carbon dioxide stick with some success.

Steiner⁴ advises that the cautery in most instances offers the best results in the treatment of the bleeding telangiectases.

Van Wegenen²⁷ used thrombokinasase to check the bleeding, and administered calcium chloride or calcium lactate. Cauterization had been tried. Injection of hot water into the base of the lesions on the tongue was suggested by him for a patient who had been bleeding from the tongue and nose for some time.

Rendu/

Rendu¹³ used for the epistaxis antipyrin, 50 gms.; tannin, 1 gm.; sugar, 10 gms.

Goldstein² gives calcium chloride, 15 gr. three times daily in cinnamon water. No general treatment seems to be effective, according to him, owing to the congenital developmental defect of the vascular system inherent in these patients. Local treatment may reduce the number and severity of the haemorrhages and improve the general condition of the patient.

East⁸ writes that the only really effectual method of stopping the bleeding is cauterization of the bleeding part. Increasing the coagulability of the blood with various drugs does little good when the fault is in the vessels themselves.

Drugs are good to combat the secondary anaemia which tends to promote and prolong haemorrhage, and thus set up a vicious circle, as was pointed out by Weber⁷.

When the haemorrhage is checked iron and arsenic are indicated for the anaemia.

AUTHOR'S CASE.

A man, J.J., aged forty years, joiner by trade, presented himself at the Royal Infirmary, Edinburgh, complaining of severe epistaxis and dyspnoea on exertion. He was admitted to the ward under Professor G. Lovell Gulland, C.M.G., on the 24th January 1927.

Epistaxis/

Epistaxis had occurred for twenty years with increasing severity and for the last two years the patient has had palpitation and dyspnoea on exertion.

HISTORY.

About twenty years ago patient started bleeding from the nose, this occurred occasionally only after sneezing or washing his face, or other slight traumatism. For the last two months epistaxis has occurred daily and has started spontaneously. He has been receiving treatment from his doctor for ten years, but the bleeding has gradually increased in severity. For twenty years or so the patient has had haemorrhoids, these only rarely bleed. In 1925 he had intermittent diarrhoea throughout the year. The haemorrhoids bled very little during this time. For the past year he has been very constipated and in consequence has been losing blood from the haemorrhoids more freely. Straining at stool on account of his constipation brought on epistaxis at times. He finds that if he loses much blood from the haemorrhoids nosebleeding was considerably lessened.

During the last two years the least bit of exertion has brought on palpitation with a heavy thumping in his chest. There was also dyspnoea, which ceased with the palpitation after resting for some time. Patient is kept awake by throbbing in his ears.

Appetite/

Appetite is good and he has only vomited once, about two years ago. He is troubled with flatulence.

Sometimes epistaxis occurs during sleep when the patient will swallow a quantity of blood; this causes a sense of nausea all next day and prevents eating.

Patient has not been losing weight or muscular strength.

Patient does not smoke or drink.

PREVIOUS HISTORY.

Measles at about the age of 10 years is the only ailment patient can remember having.

He has no history of alcoholism, lead poisoning, or syphilis.

Patient was examined in the Ear, Nose and Throat department in 1917 because of nasal obstruction.

Examination at that time showed small telangiectases on both sides of the nasal septum. The septum was irregular, and the middle conchæ were enlarged slightly. No treatment was given.

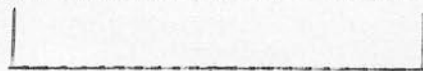
FAMILY HISTORY.

Epistaxis has been common in the family and can be traced back on both sides.

FAMILY TREE. /

FAMILY TREE.

Great Grandmother. Great Grandfather.

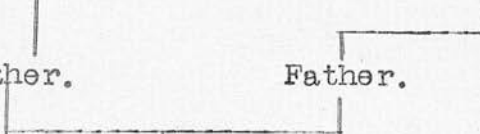


Grandmother. Grandfather. Grandmother Grandfather



Mother.

Father.



Sister. Sister. Patient.

Brother. Sister.



Daughter.

Son.



Note: Red type indicates those who were affected with haemorrhagic telangiectases.

The grandmother on the mother's side had red spots on the face. Haemorrhages occasionally occurred from some of these.

The patient's mother had telangiectases and epistaxis to a greater degree than he has, and the haemorrhages were severer. She died of pernicious anaemia at the age of fifty-six years.

His sister has some spots on her face but epistaxis is of a milder form than his. She has two daughters/



FIG I.

daughters and one son, who is the eldest, and is 14 years old. They have not suffered from epistaxis up to date.

His brother was drowned at 17 years of age.

Both his other sisters are alive and well and show no signs of the disease. They are both married. One has three sons, the eldest living, 14 years old. None have suffered from nosebleeding. The other has a son of three years of age, who has had no epistaxis.

His son has one spot on the face and has epistaxis from the least trauma.

GENERAL APPEARANCE.

Patient looks sallow and anaemic. The mucous membranes of his gums and conjunctivæ are pale. There are no signs of jaundice or oedema.

On the face there are about fifteen bright red spots, more on the right cheek than on the left one. There is one on the side of the nose. There are (Fig I) several on the lower lip and two on the right side of the tongue near the tip. On the hard palate there are two small ones and one under the nail of the middle finger on the right hand, also one under each nail of the index and ring fingers on the left hand which have only recently appeared. There are no spots on the body or legs.

The/

The spots are level with the skin and vary from pinpoint up to about two millimetres in diameter. They disappear on pressure. The patient cannot remember when the spots first appeared, and has not noticed any increase in the size or number of them on the face. His mother never remarked about any spots on his face when he was a boy.

The spots on his face only bleed when they are cut in shaving and the bleeding is very easily controlled. Bleeding from the lip, due to trauma while eating, is more frequent. This is also very easily controlled.

Strong pulsations of the carotids can be seen in the neck.

PULSE.

The blood pressure was $\frac{128}{58}$.

The pulse is of the water hammer or Corrigan type. The pulse pressure was about 70 as a rule with slight variations from day to day.

HEART.

The heart is normal in size. The apex beat is inside the nipple line and is plainly visible. On palpation there was a sense of heaving, but no sensation of a thrill all over the precordial area.

AUSCULTATION. /

AUSCULTATION.

Mitral area. A blowing systolic murmur can be heard at the apex, replacing the first sound and propagated into the axilla.

Aortic area. The systolic murmur can be heard in this area also, but is not so loud as in the mitral area.

The second sound is closed.

Pulmonary area. The first sound in the pulmonary area, is indistinct, and is replaced by a murmur. This sign is common in cases of anaemia and is probably due to that cause.

Tricuspid area. The sounds in this area are indistinct but no murmur was heard.

Bruit-de-diabie or haemic murmurs can be plainly heard over the vessels in the neck.

LUNGS.

Inspection. Chest moved freely and equally on respiration.

Palpation. The movements of the chest were verified. Vocal fremitus was normal.

Percussion. /

Percussion. Resonance was normal all over the chest.

Auscultation. The breath sounds were vesicular. No adventitious sounds were heard.

ABDOMEN.

Inspection. The abdomen moved evenly on respiration. No abnormal swellings or bulgings were seen.

Palpation. There was no rigidity of the abdominal muscles, and no tenderness on pressure. The Spleen and Liver were normal in size, and the Kidneys were impalpable. Internal and external haemorrhoids were present, which were tender to the touch.

URINARY SYSTEM.

Bladder functions are normal. Urine at no time contained abnormal constituents.

NERVOUS SYSTEM.

Examination of the eyes showed that the pupils were equal and reacted normally to light and accommodation. There was no nystagmus present.

Superficial and deep reflexes were normal.

Sensation was unaltered and the locomotory system showed no change.

BLOOD. /

BLOOD.

The coagulation time is normal.

Estimation gave the following results:-

1st drop.	2 mins.	55 seconds.
2nd drop.	1 min.	20 "
3rd drop.	1 "	5 "
4th drop.	1 "	10 "

The film shows red blood corpuscles with a small haemoglobin content, some appearing like a ring. Poikilocytosis and anisocytosis were also present. No normoblasts could be found.

The white blood corpuscles were normal.

The blood count was taken from time to time.

It shows a fairly severe secondary anaemia.

<u>Date.</u>	<u>R.B.C.</u>	<u>W.B.C.</u>	<u>Hb.</u>	<u>C.I.</u>
24.1.27	2,050,000	5,700	18%	.45
2.2.27	2,590,000	4,000		
5.2.27	2,800,000	8,000	18%	.33
11.2.27	3,350,000	4,200	30%	.45
17.2.27	2,800,000	9,000	45%	.8
24.2.27	2,660,000	4,600	36%	.7
1.3.27	3,620,000	5,200	38%	.53

PROGRESS /

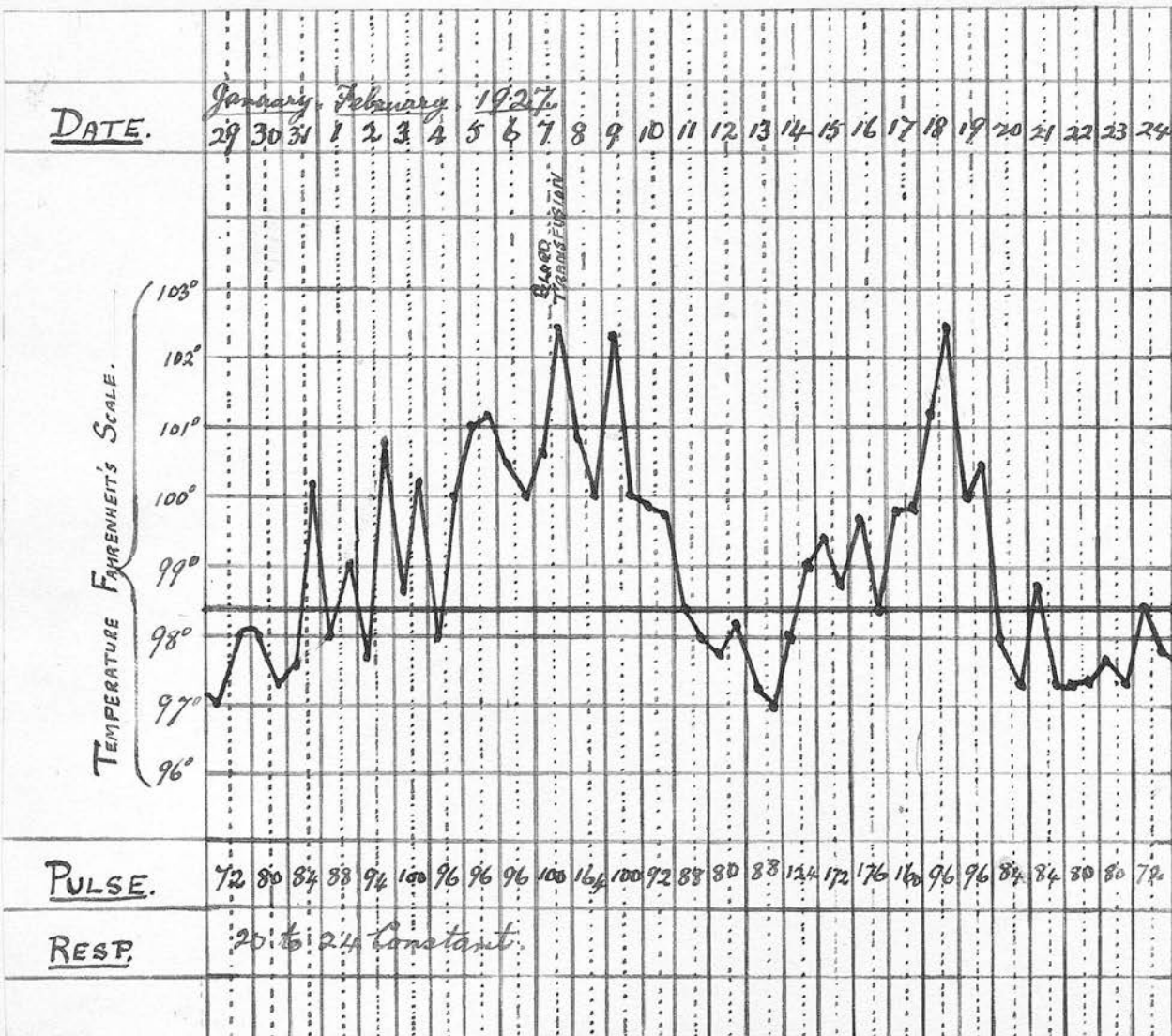


Fig II.

PROGRESS WHILE IN HOSPITAL.Epistaxis.

This symptom has gradually diminished until it has practically ceased.

Temperature.

On admission, 24th January 1927, the temperature was normal. On 1st February it began to swing. For ten days it fluctuated about 101°F , reaching as high as 102.5°F . on the 7th February, when blood transfusion was resorted to. Sixteen ounces of blood were given.

The temperature dropped to normal. After four days it again rose in a similar manner. Five days later it again dropped to normal, and has remained at this level.

(See Chart - Fig. II.)

Pulse.

With each rise of temperature a considerable quickening of the pulse occurred as will be seen from the chart (Fig. II.).

The tachycardia started and ceased gradually with the rise and fall of the temperature.

SPECIAL INVESTIGATIONS.

Blood was never found in his urine, but his faeces were never free from occult blood.

The /

The blood Wassermann test was taken and was found to be negative.

Sputum.

An examination of the sputum showed no tubercle bacilli. The organisms present were: staphylococcus albus; pneumococci; diphtheroids; and a very scanty growth of micrococcus catarrhalis. There were a small number of polymorphs and mononuclear cells.

On the 2nd February 1927, patient was sent to the Ear, Nose and Throat department. Areas of telangiectases and dilated vessels were noted on each side of the septum.

ELECTRO-CARDIOGRAMS.

During the period of tachycardia an electro-cardiogram was taken, and another when the heart had settled down. The tracing illustrating the tachycardia was taken on 16th February and is shown in Fig. III.

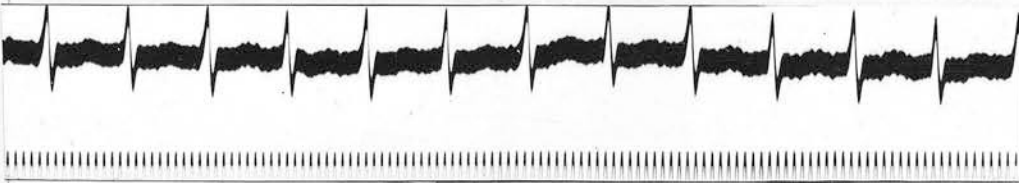


Fig. III.

On the 23rd February when the rhythm of the heart was normal a second tracing was taken, Fig IV.

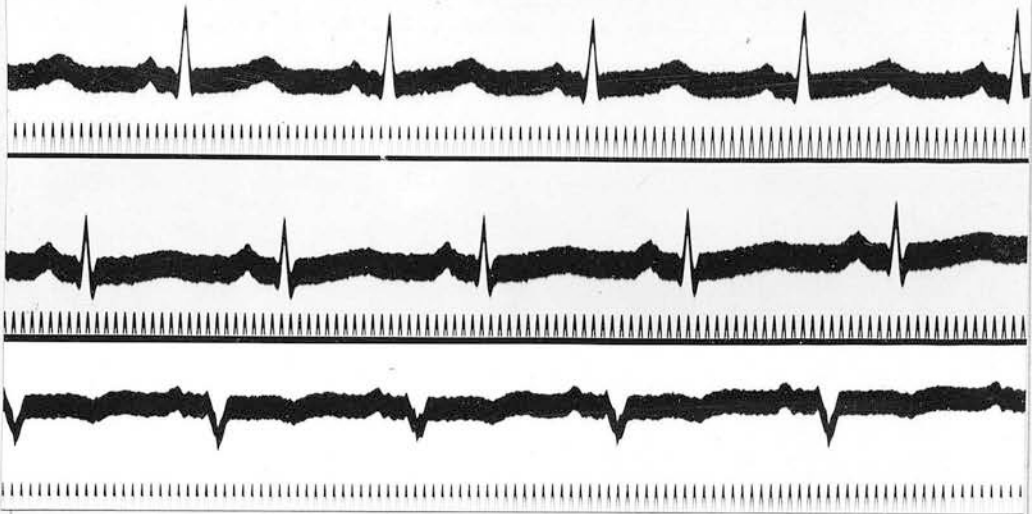


Fig. IV.

TIME.

28.57 vibrations equal to 1 second. 1 mv. = 1 cm.

Electro-cardiogram Fig III.

In the first tracing (Fig III) Lead II was employed. The rate at this time was 171 beats/min., but the tracing showed that the tachycardia was of sinus origin as the complexes had a normal form.

Electro-cardiogram Fig IV.

Three tracings are shown. The upper lead I, the middle lead II, and the lowest lead III. Here the curve is also normal, and the rate has dropped to 78 beats / min.

These tracings show a left ventricular preponderance. The P-R interval is normal, being 0.17 sec.

The/

The normal range is 0.12 to 0.18 sec. This shows that there is no delay in the impulse passing from auricle to ventricle.

TREATMENT.

On the 27th January 1927, iron and arsenic were administered for the Anaemia. This improved with diminution of the attacks of epistaxis.

On the 7th February patient's condition became so critical that sixteen ounces of blood were given by transfusion.

After the examination in the Ear, Nose and Throat department, cocaine and adrenaline were applied to the septum of the nose and the dilated vessels were cauterised with the electro-cautery.

Strips of gauze smeared with ointment were inserted for a few days.

The haemorrhoids were treated by the injection of pure carbolic acid. Three injections were given at intervals of a week. The bleeding from this source has practically stopped.

DISCUSSION OF CASE.

The only aetiologic factor which the patient shows is the hereditary one, i.e. the congenital developmental defect in the capillaries and venules.

Unfortunately/

Unfortunately for the patient the history reveals the disease in both branches of the family. The father having escaped the disease illustrates that a generation may miss being affected. The mother is said to have died of pernicious anaemia, but this might have been a very severe secondary anaemia.

The patient's daughter is by his first wife, and she shows no sign of the disease. His present wife, the second one, is a second cousin. This woman's son has nosebleeding and one spot on his face.

This case is very typical of the disease. The epistaxis started, perhaps, a little later in life than is usual. The fact of there being no history of any bleeding until he was twenty years old and the normal coagulation time exclude the possibility of this being a case of haemophilia. The hereditary nature is well shown by the family tree. The bleeding haemorrhoids undoubtedly accelerated the onset of the severe secondary anaemia, although the epistaxis had so increased in severity that the call for treatment would not have been long delayed even if they had not been present.

Bleeding from any other site never occurred spontaneously, the lip bled at times due to trauma caused by eating hard food such as toast, and from the face only after cutting an angioma with the razor.

The respite from nosebleeding experienced by the/

the patient after a loss of blood from the haemorrhoids was due, in all probability, to a lowering of the blood pressure on this account.

The sudden rises in the temperature with an abnormally rapid pulse may have been the result of a haemorrhage in some undiscovered area, possibly internal. An infection of some sort might have been the cause, although there is no definite evidence of this. No sign of an internal haemorrhage was found. The haemorrhage may have taken place however into the muscles, as telangiectases often occur in these sites in this disease. This is the most likely explanation as, at this time, the patient experienced considerable pain in the muscles of his legs.

The occult blood which was constantly found in the faeces could have come from the haemorrhoids or from the small quantities of blood swallowed by the patient from time to time, arising in the nose and running backwards into the throat.

The possibility of an infection causing the disturbance is borne out by the fact of a sudden rise in the white cell count to nearly double, although a rise is known to take place after severe haemorrhage; also by the fact that an individual with such a marked anaemia, and in such a low vital state as the patient was in, would be very liable to infection.

TREATMENT. /

TREATMENT.

The treatment which was carried out in this case was an attempt to prevent epistaxis by cauterization, and then by iron and arsenic to combat the severe secondary anaemia which had resulted.

Since the patient had his nose cauterized, his epistaxis has practically ceased, a very small bleeding occurring rarely, and in consequence he is improving rapidly.

The treatment of the haemorrhoids has also practically eliminated loss of blood from that source.

PROGNOSIS.

Judging by the progress and good response to treatment in this case, the prognosis is hopeful.

The epistaxis has now been absent for about six weeks and one is hopeful that this will continue.

The blood shows a good response to the iron and arsenic treatment, in the progressive rise in the red cell count, which has improved to the extent of a million in about a month.

GENERAL DISCUSSION.

The hereditary form of the disease appears to be rarer than Williams¹ would have us believe. Undoubtedly some infectious diseases, principally syphilis, /

syphilis, and intoxications such as alcoholism and plumbism play a part in its production. They attack the vascular system causing degeneration of the arteries with consequent weakening of their walls, and telangiectases appear. Some cases have been associated with one or other of these causes.

Glandular mischief has also been ascribed as a cause and cases have been noted to substantiate its aetiologic significance.

Not one of these different factors has been present consistently enough to be able to seriously attach much importance to it as a causative agent in the hereditary form. Besides, there are a number of cases in which all the infectious diseases and intoxications mentioned as probable causes, have been definitely excluded. This is so in the case recorded by the author.

The upset of the balance of the internal secretions as a cause, naturally cannot be excluded, because minor glandular defects, which may in themselves be sufficient to cause vascular changes, cannot be recognized. Sometimes the glandular upset is severe enough to produce definite signs and symptoms such as in exophthalmic goitre and acromegaly. Cases associated with both the above diseases have been recorded.

If this aetiologic factor was accepted then naturally/

naturally the glandular weakness would have to be admitted to be hereditary, i.e. transmitted to the off-spring. Diseases of the endocrine glands have not been generally admitted to be hereditary, so that no more weight can be given to this cause than to the others.

The most rational aetiologic factor appears to be that of a congenital developmental error in the vessels, just as other developmental deformities are sometimes handed on. The abnormality may be more pronounced in some than in other members of a family, while some may escape altogether. This is brought out by the patient's family very well. He himself is severely affected, his sister is much less so, while the other two sisters are exempt.

Again histories recorded show that a whole generation may escape, only for the disease to appear in a later one, while again it appears to have entirely died out in some of the branches.

Cases with no family history may be acquired or may be recurrences after a period of latency.

The fact that so many different causes have been described in the acquired form suggests the possibility that they are not the real cause, but that they are two separate conditions occurring in one individual - the infection causing the hereditary weakness to become apparent.

The/

The chief sign of the disease is epistaxis. In fact this is the cause of the other signs and symptoms and is also the reason that the patient seeks medical aid. The epistaxis generally starts in early childhood and usually increases in severity up to middle life, very rarely does it decrease with age, and rarer still does it cease.

An acquired telangiectasis is quite common and a definite cause can usually be found. The cab driver's complexion is well known and is generally the result of alcoholism coupled with exposure to the weather. The mucous membranes never seem to be affected in this type as nosebleeding never occurs.

Although nothing is known about the cause of the familial abnormality, telangiectases certainly do appear in association with a number of conditions. These are undoubtedly cases of the acquired form. It would be interesting to follow up such cases and see if the disease was transmitted to the offspring. In the acquired type possibly the action of a toxin weakens the wall of the capillary by causing degeneration, and the pressure of the blood in the capillary brings about the dilatation.

The increase in the severity of the bleeding and in the number of the telangiectases, as the sufferer gets older, could be explained by the vascular changes and/

and the rise of blood pressure which are of normal occurrence with age.

The profuseness of the haemorrhage throughout the disease is due to the lack of the muscular and elastic coats of the capillaries. Thus retraction and consequent narrowing, or even actual occlusion, of the vessels takes place imperfectly.

Before the character of the lesions was recognised this disease was called hereditary epistaxis. Pearson²⁸ and Aitken²⁹ have recorded cases of hereditary haematuria which might possibly have been cases of hereditary telangiectasis affecting the urinary tract. The histories of the other cases however make this very improbable as in none of them was blood found in the urine, although the capillaries in the urethra of one patient were found, at the necropsy, to be in a telangiectatic state.

Bleeding except from the nose, seems rarely to have taken place spontaneously, traumatism being a necessary factor. The mucous membrane of the nose is very liable to slight trauma due to sneezing, or blowing the nose, or even rubbing the nose, so that it is questionable if even here bleeding may not be initiated by trauma; this could be of a very slight degree as the nasal mucous membrane is very delicate.

Although hereditary telangiectases is the simple form/

form of the angiomata, the other form being cavernous, it is very rare to get both types of angiomata associated in the same individual. East⁸ reports a case in which a woman had a cirroid enlargement of the arteries of the right arm, with great dilatation of the veins of the hand, as well as telangiectases.

The true haemangioma, MacCullum⁵ tells us, is distinguished from a mere dilatation of capillaries or venules belonging to the general circulation by the fact that its blood channels grow independently, without regard to the laws which govern the distribution of such vessels. It therefore forms a mass which is somewhat withdrawn from the general circulation, and is of the nature of a neoplasm. From this it would appear that the two are distinct diseases and would account for the rarity of both appearing in the same person.

The cirroid angiomata are considered to be border-line conditions between the two.

The severe anaemia which develops with its concomitant weakness, dyspnoea, etc., makes this disease a serious one.

Recovery from the disease may take place, as is shown in one of the cases reported by East⁸:-

A woman, aged forty-four years, had had a good deal of nosebleeding. This had been sufficiently severe to send her to hospital. Lately she has been free/



free from this and no naevi are to be seen on the lower part of the septum.

The actual haemorrhage is rarely the cause of death, only three instances of the kind being recorded. Death is usually due to an intercurrent disease.

Due to the ignorance of the aetiology of the disease, no specific treatment has as yet been found.

Thermo-cautery is the only method which has as yet given any satisfactory results in stopping the haemorrhage, and even this has failed, in some cases to stem the attacks of epistaxis.

Drugs can only be of use in the treatment of the symptoms without in any way improving the primary lesion.

S U M M A R Y.

AETIOLOGY.

The disease is most probably due to congenital defective development of the blood vessels with epistaxis, commencing in childhood, and increasing in severity with age. The telangiectases appearing later and also increasing in size and numbers with age.

The disease occurs in males and females equally and is transmitted by both, although it appears to be carried on more through the females than the males.

PATHOLOGY. /

PATHOLOGY.

The lesions are a dilatation of the capillaries and venules due to an absence or deficiency of the muscular and elastic coats. It affects both skin and mucous membranes - the septum of the nose being especially susceptible.

SYMPTOMS.

The main one is epistaxis. The anaemia resulting from the continual drain on the blood from this recurrent epistaxis is the cause of the appearance of all the other symptoms, the chief among which are dyspnoea, palpitation, and weakness, on exertion.

PROGNOSIS.

This is very unsatisfactory, as recovery is a rare occurrence. Death is seldom due to the haemorrhage or anaemia, but usually to an intercurrent disease such as pneumonia, etc.

TREATMENT.

This consists in attempts to prevent haemorrhage, and no satisfactory method has as yet been arrived at. Thermo-cautery has proved the most satisfactory. All other treatment is purely palliative, and is an attempt to improve the anaemia which is frequently very severe.

C O N C L U S I O N S .

- (1) The cause of the disease is unknown.
 - (2) It has a hereditary nature, and appears in both sexes. It can be transmitted by both male and female.
 - (3) There is a tendency to increase in severity with advancing years.
 - (4) Recovery is rare.
 - (5) It is rarely a primary cause of death.
 - (6) There is no satisfactory treatment. Treatment at present is purely symptomatic.
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REFERENCES.

1. Williams, C.M.: Arch. Dermat. and Syph. (July) 1926 - 14 - 1.
2. Goldstein, H.I.: Arch. Int. Med. (Jan) 1921 - 27 - 102.
3. Hanes, F.M.: John Hopkin's Hosp. Bull. 1909 - 20 - 63.
4. Steiner, W.: Arch. Int. Med. (Feb) 1917 - 19-194.
5. MacCullum: Textbook of Pathology. 1922 - 963.
6. Legg, J.W.: Lancet. 1876 - 2 - 856.
7. Weber, F.P.: Brit. J. Dermat. 1908 - 20 - 159.
also Proc. Roy. Soc. Med. Lond. 1907 - 1 - 44.
8. East, C.F.T.: Lancet. 1926 - 1 - 332.
9. Stokes: Am. Jour. Med. Sc. 1915 - 149 - 669.
10. Majocchi, D.R.: Arch. delle Scienze della
Institue di Bologna. 1905.
11. Head, G.D.: Arch. Int. Med. (July) 1917 - 20-24.
12. Babbington: Lancet, London. 1865 - 2 - 362.
13. Rendu: Gaz. d. Hop. 1896 - 49 - 1322.
14. Ballantyne, A.J.: J. Glasgow M.J. 1908 - 70-256.
15. Kennan, R.H.: Med. Press and Circ. 1902 - 33-458.

16. Fox, T.C.: Brit. J. Dermat. 1908 - 20 - 145.
17. Josserand: Bul. Soc. Med. d. hop. de Lyon. 1902 -
1 - 244.
18. Gjessing, E.: Hospitalstudende. 1915 - 8 - 1151.
19. Sequiera, J.H.: Proc. Roy. Soc. Med. London.
1912 - 6 - 128.
20. Anderson, W.: Brit. J. Dermat. 1898 - 10 - 114.
21. Ullmann, C.: Arch. f. Dermat u Syph. 1896 - 35.
22. Osler : Principles & Practice of Medicine. 1925
VII. 615.
23. Crocker: Atlas, pl. 71, Fig I.
24. Laffont: Presse Méd. 1909 - 17 - 763.
25. Mekie, E.C.: Brit. Med. Jour. (March 5) 1927.
p. 423.
26. Bruck, F.: Med. Klin. Berl. 1917 - 13 - 505.
27. Van Wegenen, C.D.: Med. Rec. 1912 - 109 - 81.
28. Pearson: Lancet. 1904 - 1 - 91.
29. Aitken: Lancet. 1909 - 2 - 444.
30. Ribbert: Virch. Arch. 1898. cli, 381.
